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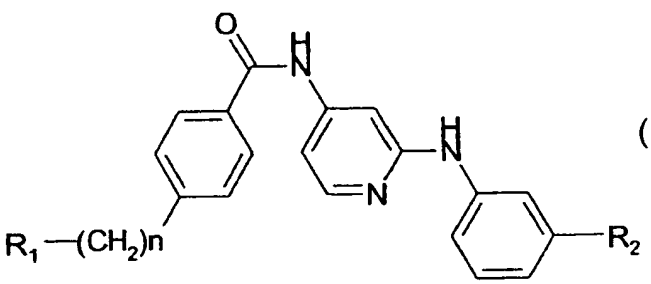
(54) Title: PROTEIN TYROSINE KINASE INHIBITORS



(I)

(57) Abstract: The present invention relates to compounds of the Formula I, the pharmaceutically acceptable salts and stereoisomers thereof, which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compositions which contain these compounds, and methods of using them to treat tyrosine kinase-dependent diseases and conditions in mammals:wherein n is an integer, preferably n is 1;wherein R_1 and R_2 are independently selected from the group consisting of:wherein R3 is selected from the group consisting of H; alkyl; alkenyl; alkynyl; halogen; aryl; heteroaryl containing N, O, or S; the aryl and heteroaryl may be further substituted with halogen, an alkyl, alkenyl, and alkynyl; NZ_1Z_2, wherein Z_1 and Z_2 are independently selected from the group consisting of H and alkyl; and (CO)Y wherein Y is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heteroaryl containing N, O, or S, and the aryl and heteroaryl may be further substituted with halogen, alkyl, alkenyl, and alkynyl; andwherein R_4 is selected

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Protein Tyrosine Kinase Inhibitors

Field of the Invention

The present invention relates to compounds which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compositions which contain these compounds, and methods of using them to treat tyrosine kinase-dependent diseases and conditions in mammals.

Background of the Invention

Throughout this application, various references are cited in parentheses to describe more fully the state of the art to which this invention pertains. The disclosure of these references are hereby incorporated by reference into the present disclosure.

Tyrosine kinases are a class of enzymes that catalyze the transfer of the terminal phosphate of adenosine triphosphate to tyrosine residues in protein substrates. Tyrosine kinases are believed, by way of substrate phosphorylation, to play critical roles in signal transduction for a number of cell functions. Though the exact mechanisms of signal transduction is still unclear, tyrosine kinases have been shown to be important contributing factors in cell proliferation, carcinogenesis and cell differentiation.

Tyrosine kinases can be categorized as receptor type or non-receptor type. Receptor type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

The receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. Approximately, 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily is comprised of EGFR, HER2, HER3, and HER4. Ligands of this subfamily of receptors include epithelial growth factor, TGF-α, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-α and β

receptors, CSFIR, c-kit and FLK-II. The FLK family is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1) (Plowman et al., DN&P 7(6):334-339, 1994, which is hereby incorporated by reference).

The non-receptor type of tyrosine kinases are also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis (Bolen Oncogene, 8:2025-2031 (1993), which is hereby incorporated by reference).

Both receptor-type and non-receptor type tyrosine kinases are implicated in cellular signalling pathways leading to numerous pathogenic conditions, including a variety of cancers. For example, the Bcr-Abl tyrosine kinase is the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). Inappropriate Bcr-Abl activity is also demonstrated in murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

A variety of tyrosine kinase inhibitors have been developed for the treatment of different types of clinical conditions. See for example U.S. Patent Nos. 5,543,520 and 5,521,184.

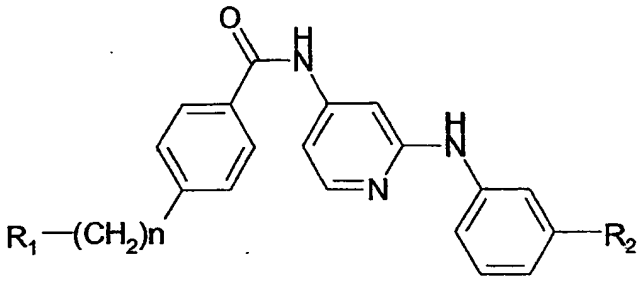
It is therefore desirable to identify additional compounds which specifically inhibit, regulate and/or modulate the signal transduction of tyrosine kinases and in particular those tyrosine kinases involved in various malignancies in order to develop novel strategies for treatment.

Summary of the Invention

The present invention relates to compounds which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compositions which contain these compounds, and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as cancer and tumor growth, and the like in mammals.

More particularly, the present invention relates to compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. The compounds are novel protein tyrosine kinase inhibitors useful in the treatment of a variety of malignancies involving inappropriate tyrosine kinase activity.

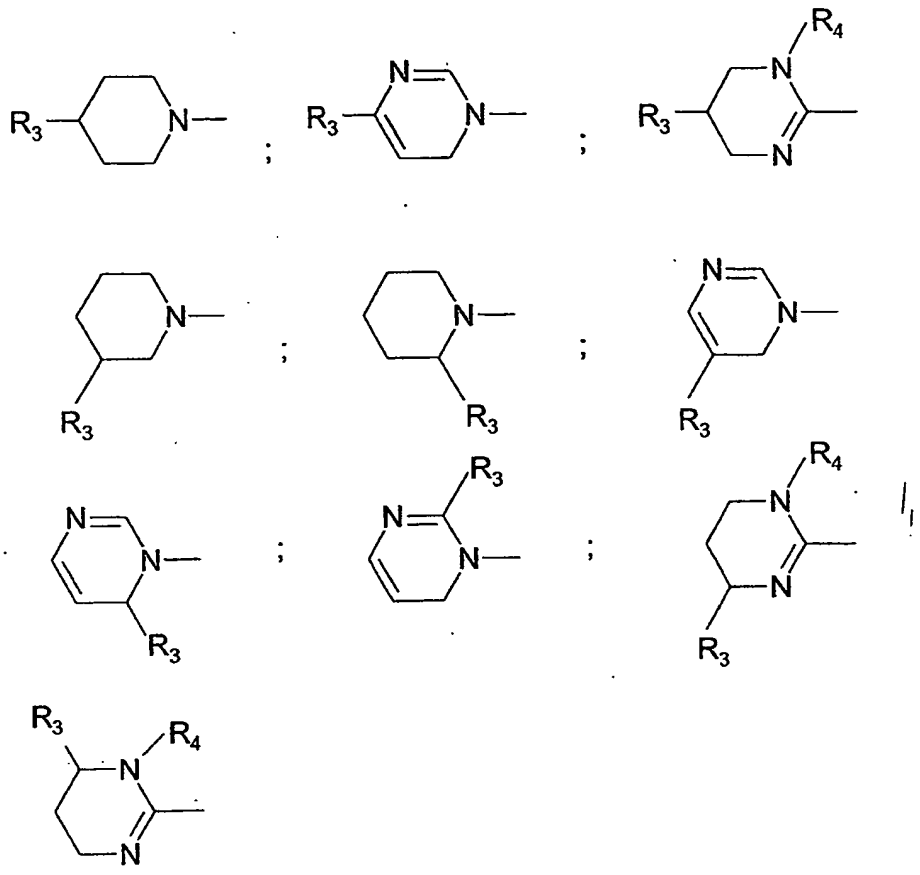
One embodiment of the present invention is illustrated by a compound of Formula I, and the pharmaceutically acceptable salts and stereoisomers thereof:



Formula I

wherein n is an integer, preferably n is 1;

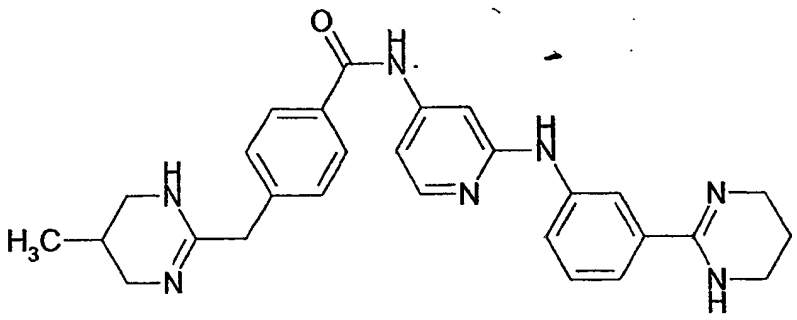
wherein R_1 and R_2 are independently selected from the group consisting of:



wherein R_3 is selected from the group consisting of H; alkyl; alkenyl; alkynyl; halogen; aryl; heteroaryl containing N, O, or S; the aryl and heteroaryl may be further substituted with halogen, an alkyl, alkenyl, and alkynyl; NZ_1Z_2, wherein Z_1 and Z_2 are independently selected from the group consisting of H and alkyl; and (CO)Y wherein Y is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heteroaryl containing N, O, or S, and the aryl and heteroaryl may be further substituted with halogen, alkyl, alkenyl, and alkynyl; and

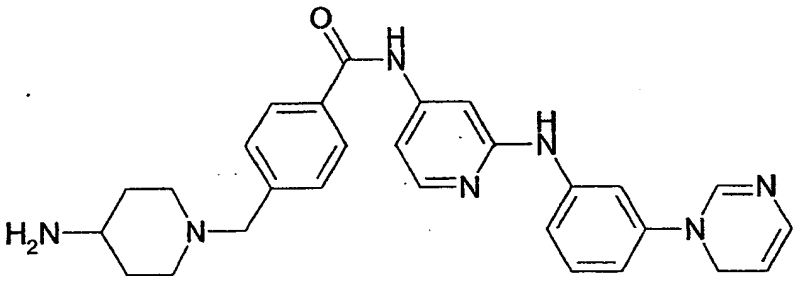
wherein R_4 is selected from the group consisting of H and alkyl.

In one aspect of the present invention, the compound is represented as formula II:



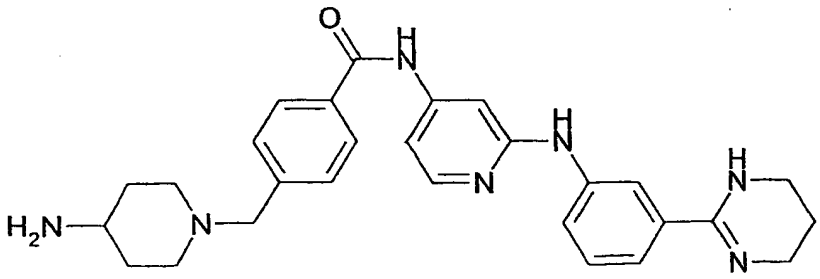
Formula II

In a further aspect of the present invention, the compound is represented as formula III:



Formula III

In a further aspect of the present invention, the compound is represented as formula IV:



Formula IV

According to another aspect of the present invention is a pharmaceutical composition which is comprised of a compound in accordance with formula I together with a pharmaceutically acceptable carrier.

According to another aspect of the present invention is a pharmaceutical composition which is comprised of a compound in accordance with formula II or formula II together with a pharmaceutically acceptable carrier.

According to another aspect of the present invention is a method of treating or preventing cancer involving inappropriate tyrosine kinase activity in a mammal in need of such treatment which is comprised of administering to the mammal a therapeutically effective amount of a compound of formula I, II, III or IV, or mixtures thereof.

According to another aspect of the present invention is a method of treating cancer or preventing cancer using a composition comprising a compound of formula I, II, III or IV, or mixtures thereof, wherein the cancer is selected from cancers of the breast, leukemias, melanoma, stomach, colon, CNS, ovarian and prostate and those listed in Table I.

According to still another aspect of the present invention is a method of treating or preventing cancer using a composition comprising a compound of formula I, II, III or IV, or mixtures thereof, wherein the cancer is chronic myelogic leukemia (CML).

According to another aspect of the present invention is a method of treating or preventing a tyrosine kinase-dependent disease or condition which comprises administering a therapeutically effective amount of a compound selected from the group consisting of formula I, formula II, formula III, formula IV and mixtures thereof.

According to yet another aspect of the present invention is a process for making a pharmaceutical composition which comprises combining a compound of formula I, II, III and/or IV with a pharmaceutically acceptable carrier.

According to another aspect of the present invention is the use of a compound of formula I, II, III and/or IV in a medicament for the treatment of a disease or condition involving inappropriate tyrosine kinase activity.

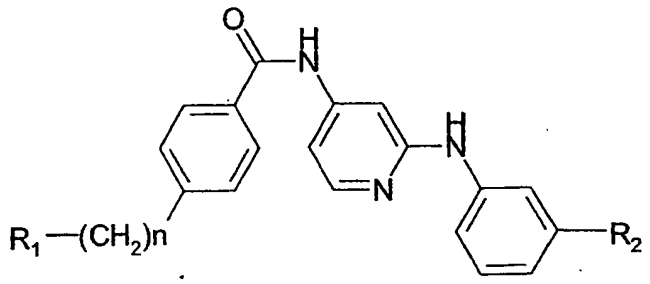
According to still a further aspect of the present invention is composition comprising a compound of formula I further comprising a second compound selected from the group consisting of an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic agent, an anti-proliferative agent, a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, and troponin-1, tamoxifen and raloxifene.

According to a further aspect of the present invention is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of formula I, II, III or IV, and mixtures thereof, or pharmaceutically acceptable salts thereof in combination with a therapy selected from the group consisting of radiation therapy and chemotherapy.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from the detailed description.

Detailed Description of the Preferred Embodiments

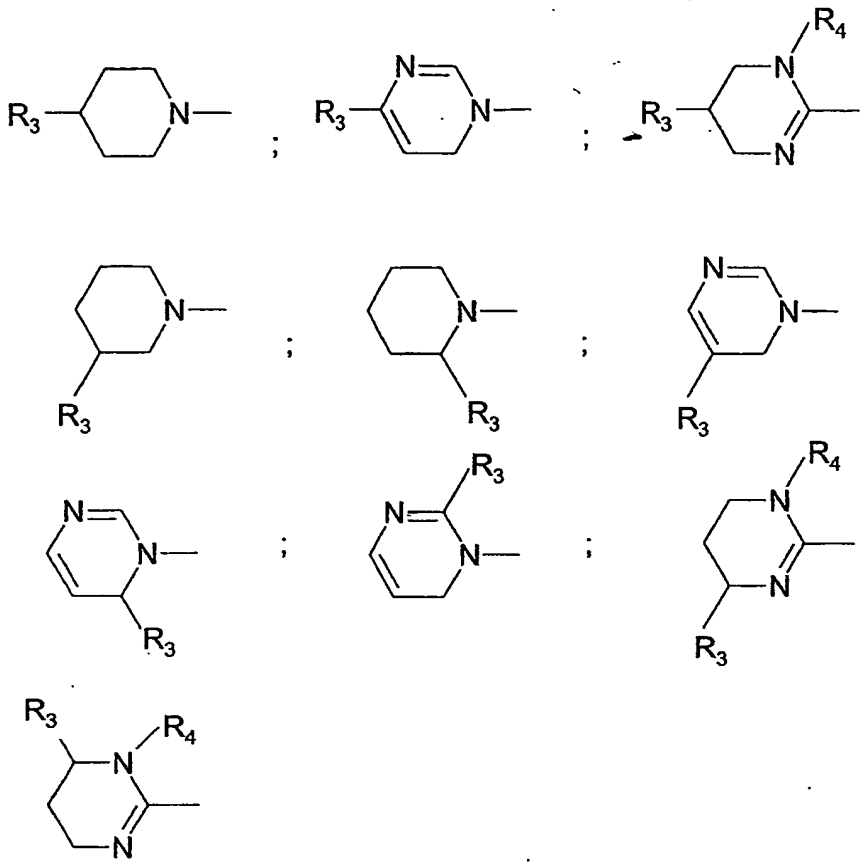
The compounds of this invention are illustrated by a compound of Formula I or a pharmaceutically acceptable salt or stereoisomer thereof, wherein



Formula I

wherein n is an integer, preferably n is 1;

wherein R_1 and R_2 are independently selected from the group consisting of:



wherein R_3 is selected from the group consisting of H; alkyl; alkenyl; alkynyl; halogen; aryl; heteroaryl containing N, O, or S; the aryl and heteroaryl may be further substituted with halogen, an alkyl, alkenyl, and alkynyl; NZ_1Z_2, wherein Z_1 and Z_2 are independently selected from the group consisting of H and alkyl; and (CO)Y wherein Y is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heteroaryl containing N, O, or S, and the aryl and heteroaryl may be further substituted with halogen, alkyl, alkenyl, and alkynyl; and

wherein R_4 is selected from the group consisting of H and alkyl.

Yet another embodiment of the present invention is a compound which is selected from the group consisting of 4-(5-Methyl-1,4,5,6-tetrahydro-pyrimidin-2-ylmethyl)-N-{2-[3-(1,4,5,6-tetrahydropyriminin-2-yl)-phenylamino]-pyridin-4-yl}benzamide (Formula II), 4-(4-Amino-piperidin-1-yl)methyl-N-{2-[3-

(6H-pyrimidin-1-yl)-phenylamino]-pyridin-4-yl} benzamide (Formula III) and 4-(4-Amino-piperidin-1-yl)methyl-N-{2-[3-(3, 4, 5, 6-tetrahydropyrimidin-2-yl)-phenylamino]-pyridin-4-yl} benzamide (Formula IV) as well as pharmaceutically acceptable salts or stereoisomers thereof.

Using an in silico assay, the compounds of the present invention have been demonstrated and predicted to have *in vitro* activity against a variety of cancerous cell types, some data are shown in Table 1. Also, while not explicitly shown, compounds of Formula II, III and IV have predicted *in vitro* activity against HIV.

Included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The present invention also encompasses a method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering to the mammal a therapeutically effective amount of a compound of Formula I. Preferred cancers for treatment are selected from cancers of the breast, colon, prostate, gastric, melanoma, ovarian and leukemias. Another preferred form of cancer is chronic myelogic leukemia (CML).

The invention also encompasses pharmaceutical compositions comprising a compound of Formula I, II, III and/or IV as well as pharmaceutically acceptable salts thereof for the treatment of HIV.

The compositions and methods of the invention can include a compound of Formula I, II, III or IV, or mixtures thereof, as desired.

Also included is a method of treating or preventing a tyrosine kinase-dependent disease or condition in a mammal which comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of Formula I. The therapeutic amount varies according to the specific disease and is discernible to the skilled artisan without undue experimentation.

Also included in the scope of the claims is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formula I, Formula II, Formula III and Formula IV in combination

with radiation therapy and/or in combination with a compound generally known for use in selected cancers and selected from the group consisting of an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic agent and an antiproliferative agent. These and other aspects of the invention will be apparent from the teachings contained herein.

"Tyrosine kinase-dependent diseases or conditions" refers to pathologic conditions that depend on the activity of one or more tyrosine kinases. Tyrosine kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion and migration, and differentiation. Diseases associated with tyrosine kinase activities include but are not limited to the proliferation of tumor cells.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E. L. Eliel and S. H. Wilen, Stereo-chemistry of Carbon Compounds, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted.

As used herein, "alkyl" is intended to include both branched, straight-chain, and cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_{1-10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear, branched, or cyclic arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on, as well as cycloalkyls such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydro-naphthalene, methylenecylohexyl, and so on. "Alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. For instance, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups may include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to 3 carbon-carbon triple bonds may be present. For instance, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups may include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydro-naphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. In cases where the

heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo. The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrahydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof.

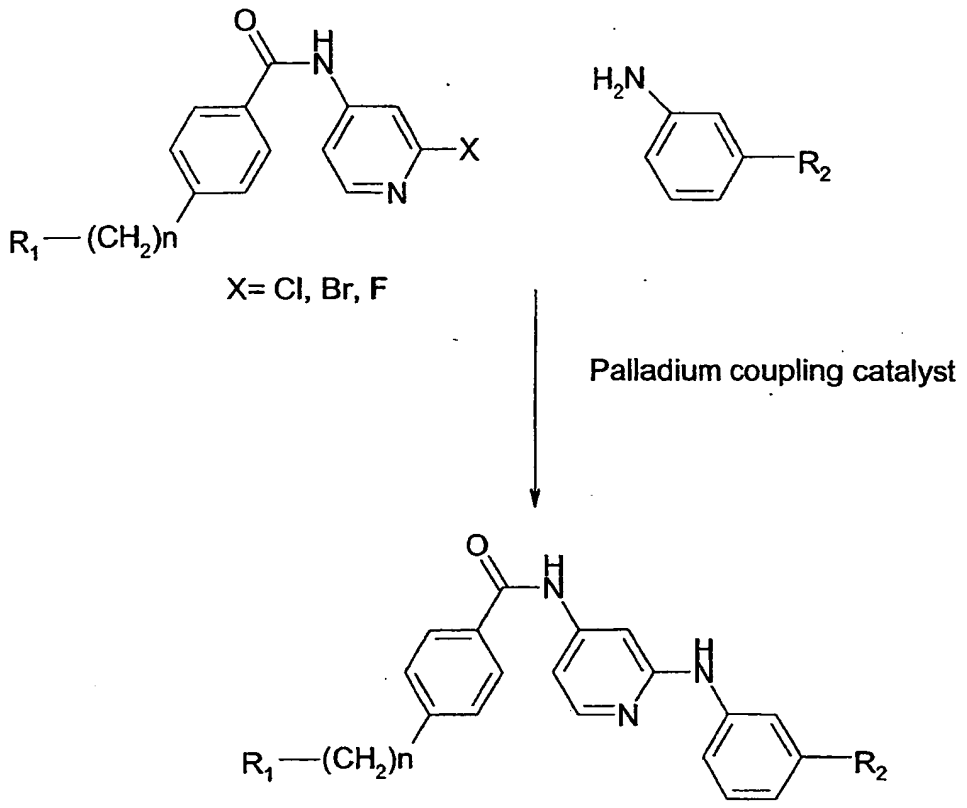
The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from

inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

The compounds of this invention may be prepared by employing reactions and standard manipulations that are known in the literature or exemplified in the experimental procedures.

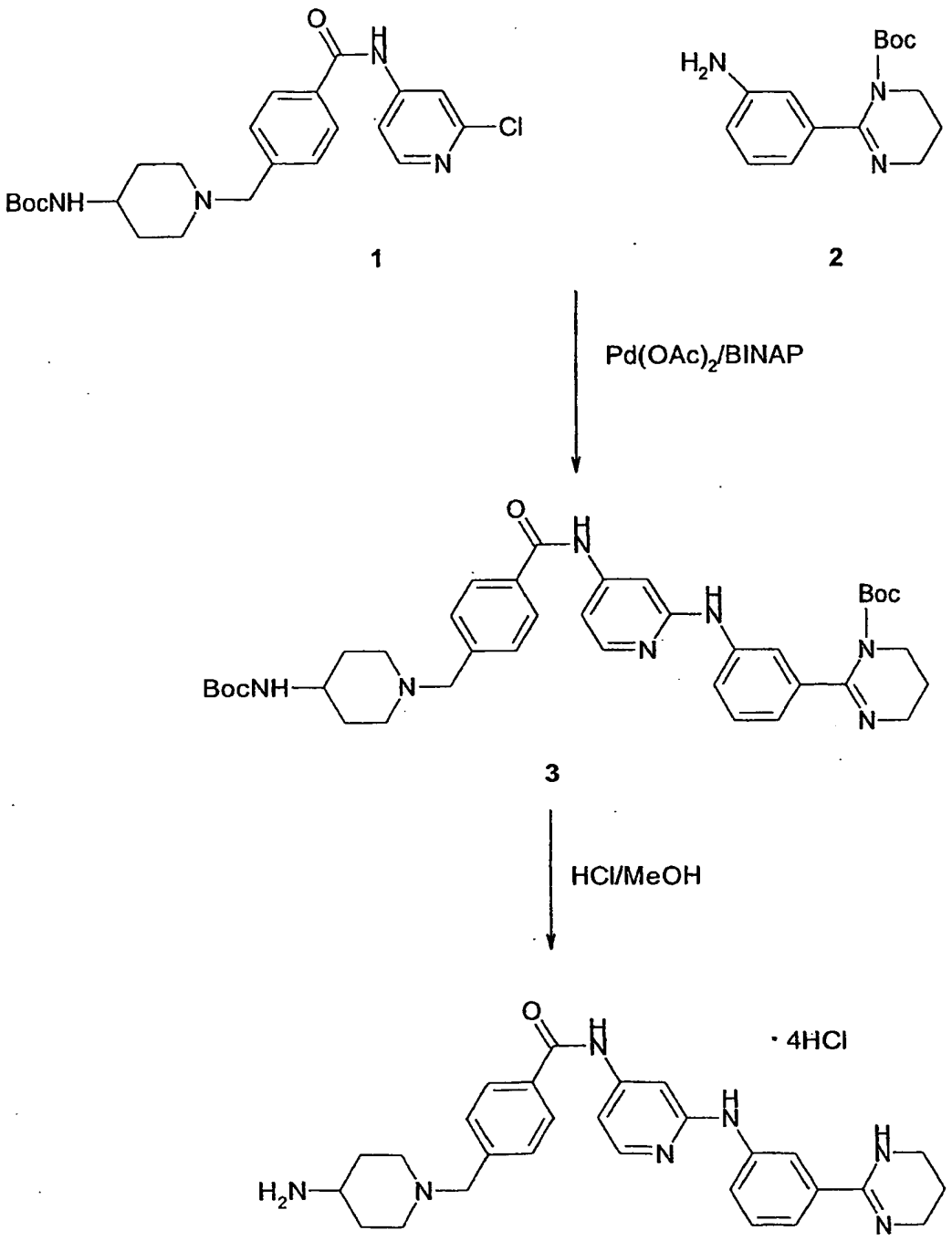
The compound of general formula I may be synthesized using a palladium-catalyzed coupling reaction as follows:



Formula I

Some suitable palladium coupling catalysts for promoting carbon-nitrogen bond-forming cross-coupling include, but are not limited to, $Pd(OAc)_2$ with BINAP (2,2'-bis(diphenyphosphino)-1,1'-binaphthyl) and $Pd_2(dba)_3$ (dba is diphenyl phosphine ferrocene) with DPPF (dibenzylidene acetone). Protecting groups may be utilized to protect the R_1 and R_2 groups during the coupling reaction and, as a result, a further step may include deprotection. As a result of deprotection, the salt of formula I may be formed. The free base may be obtained by treating the salt with a base such as, but not limited to, sodium hydroxide and sodium carbonate.

In an illustrative example, the salt of formula IV may be synthesized as shown in Scheme 1.

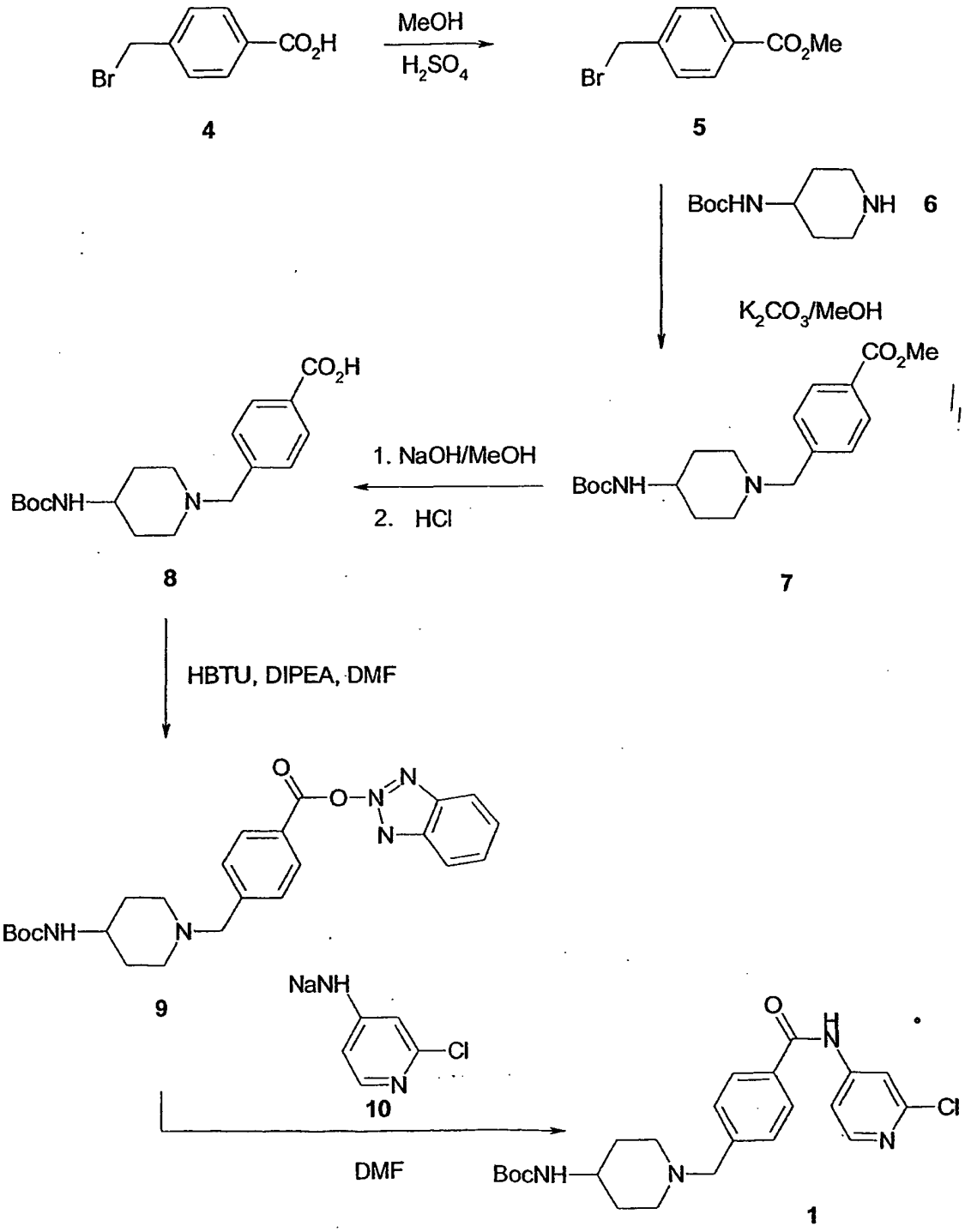


Salt of Formula IV

Scheme 1

Intermediates **1** and **2** underwent a coupling reaction in the presence of $Pd(OAc)_2$ and BINAP to yield the Boc-protected coupling product **3**. The Boc protective groups were removed with saturated HCl solution in MeOH to afford the salt of Formula IV.

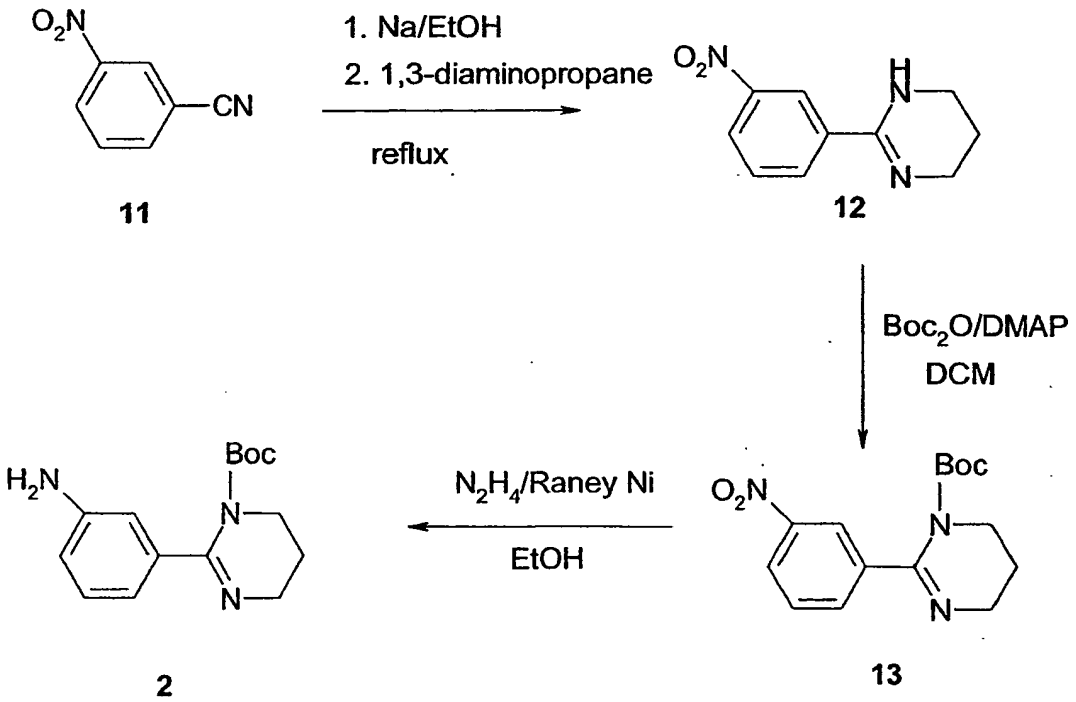
Intermediates for the coupling reaction may be prepared using various reactions known in the literature. For instance, intermediate **1** may be synthesized as shown in Scheme 2.


MeOH
H2SO4
CO2H
Br
CO2Me
4
5
BocHN
NH
6
K2CO3/MeOH
1. NaOH/MeOH
2. HCl
BocNH
N
8
7
HBTU, DIPEA, DMF
O
9
NaNH
Cl
10
DMF
1

Scheme 2

The first step for synthesizing intermediate **1** involved the esterification of 4-bromomethylbenzoic acid **4** to methyl 4-bromomethylbenzoate **5**. Methyl 4-bromomethylbenzoate **5** was then reacted with commercially available 4-boc-aminopiperidine **4** to yield compound **7**. The ester group of compound **7** was hydrolyzed to compound **8** and further reacted with coupling reagent, HBTU, and DIPEA in DMF to form the activated ester **9**. The activated ester **9** was then reacted with sodium 2-chloropyrid-4-ylamide **10** to yield intermediate **1**.

Intermediate **2** may be synthesized as shown in Scheme 3.

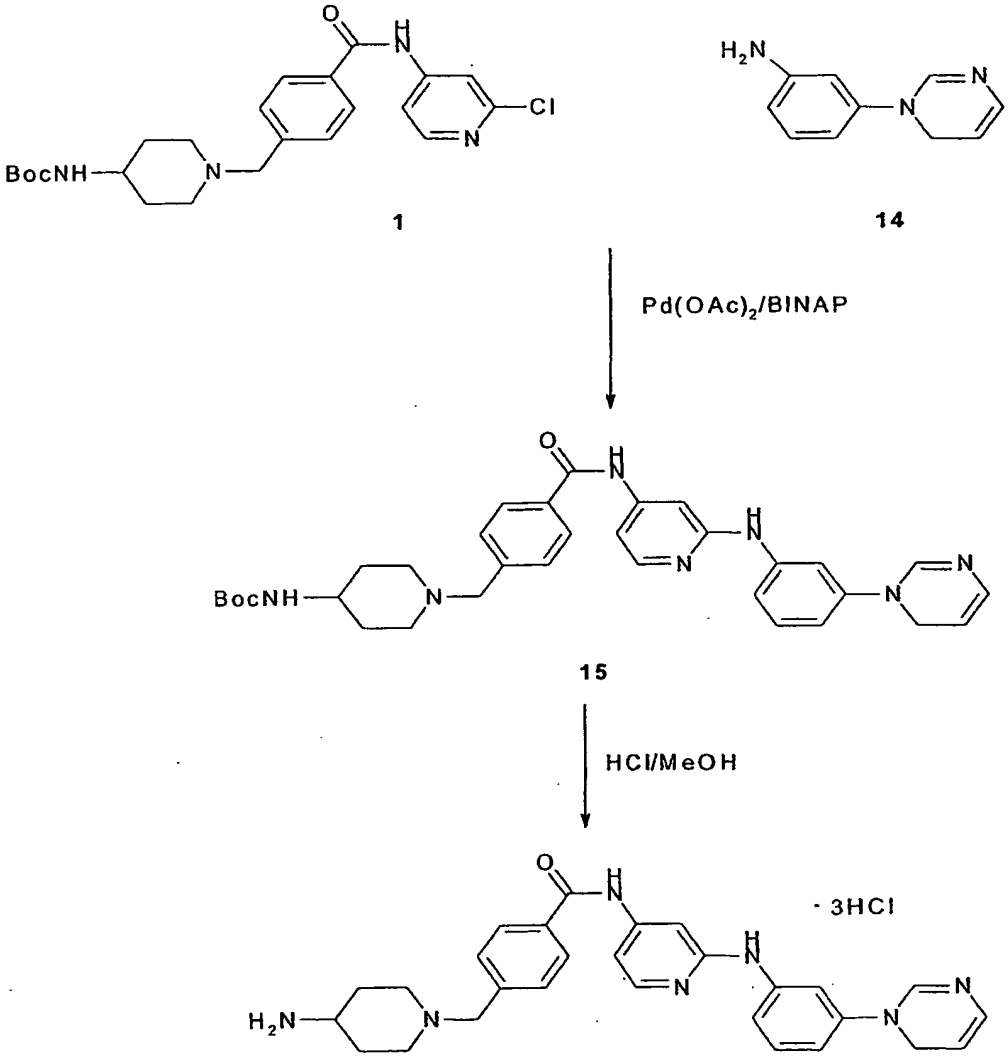


Scheme 3

For the transformation of 3-nitrobenzonitrile **11** into 3,4,5,6-tetrahydro-2-(3-nitrophenyl)-pyrimidine **12** was conducted using a procedure described in European Patent Application 0225725 A1 for 4-nitrobenzonitrile; incorporated herein by reference. 3,4,5,6-tetrahydro-2-(3-nitrophenyl)-pyrimidine **12** was

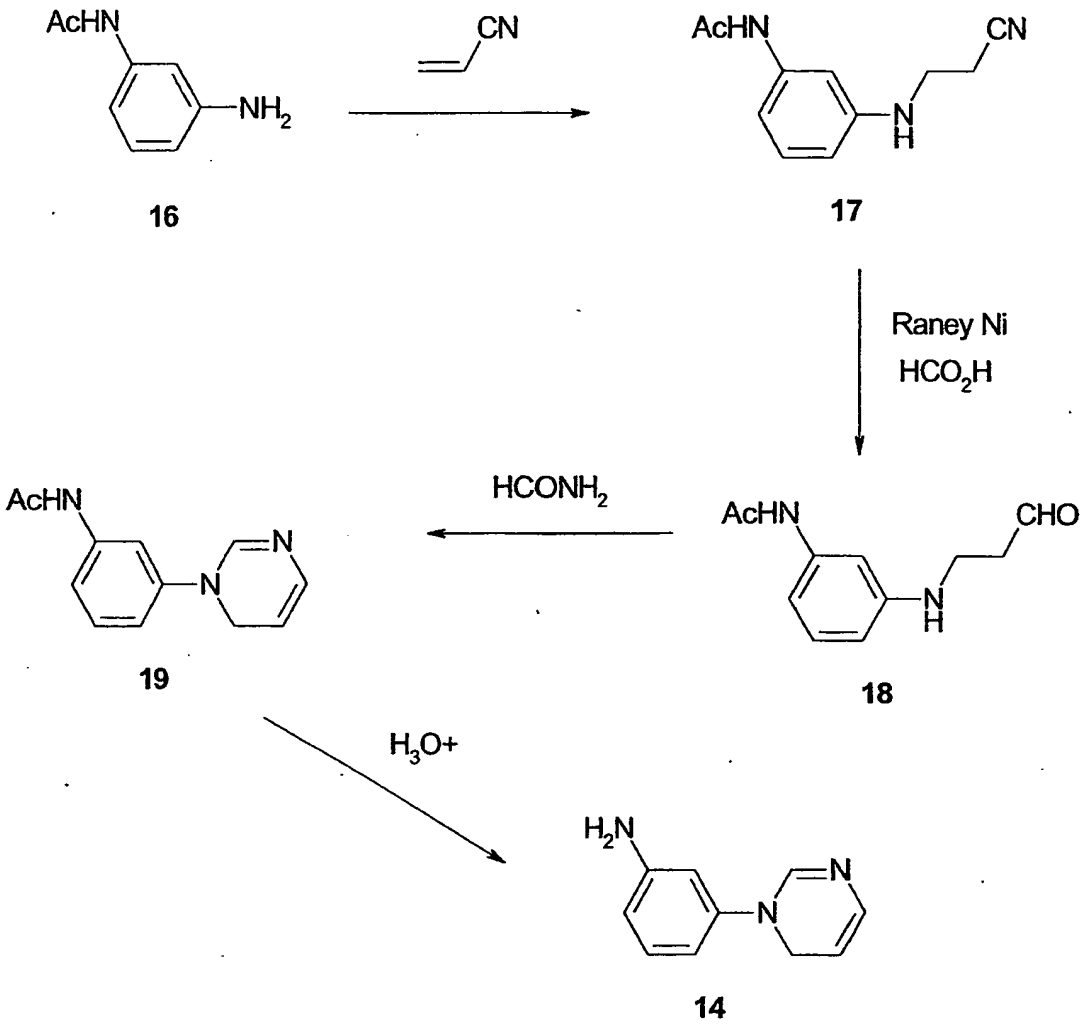
protected using Boc_2O, carried out in DCM at room temperature in the presence of DMAP as a catalyst to yield Boc-protected compound **13**, which was then reduced to intermediate **2**.

In a further example, the salt of formula III may be synthesized as shown in Scheme 4, which is similar to the reaction shown in Scheme 1.



Scheme 4

Intermediate **14** may be synthesized as shown in Scheme 5.



Scheme 5

5

The reaction of 3'-aminoacetanilide **16** with acrylonitrile yields the resultant addition product **17**. Reduction of the addition product **17** yields the aldehyde **18**. The aldehyde **18** reacts with formamide to yield the cyclic compound **19**. The cyclic compound **19** is then hydrolyzed to intermediate **14**.

The compounds of the instant invention are useful as pharmaceutical agents for mammals, especially for humans, in the treatment of tyrosine kinase dependent diseases and in particular the treatment of various cancers.

The compounds of the instant invention may be administered to patients for use in the treatment of cancer.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated.

The instant compounds are also useful in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors. The instant compounds are particularly useful when coadminsitered with radiation therapy. The synergistic effects of inhibiting VEGF in combination with radiation therapy have been described in the art. (see WO 00/61186). "Estrogen receptor modulators" refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylomithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide and N-4-carboxyphenyl retinamide.

"Cytotoxic agents" refer to compounds which cause cell death primarily by interfering directly with the cell's functioning or inhibit or interfere with cell

myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine) platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino- -13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunor- ubicin (see WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(- 3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS 188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine- -2-(6H)propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methy- -1H,12H benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H) dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide,

GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazo- le-1-carboxamide, asulacrine, (5a, 5aβ, 8aa,9b)-9-[2-[N-[2-(dimethylamino)- ethyl]-N-methylamino]ethyl]-5-[4-Hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,- 9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridiniu- m, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-py- razolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy— 9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acrid- ine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2- ,1-c]quinolin-7-one, and dimesna.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxy- cytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl) urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycer- o-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b] [1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes,

such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example).

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino-)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH1382, genistein, ST1571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo [2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)- amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, ST1571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological

or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, particularly cancers involving inappropriate tyrosine kinase activity, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific Examples. These Examples are described solely for purposes of illustration and are not intended to limit the scope of the invention. Changes in form and substitution of equivalents are contemplated as circumstances may suggest or

render expedient. Although specific terms have been employed herein, such terms are intended in a descriptive sense and not for purposes of limitation.

Examples

Methods of synthetic chemistry, protein and peptide biochemistry, molecular biology, and pharmacology referred to but not explicitly described in this disclosure and examples are reported in the scientific literature and are well known to those skilled in the art.

Example 1

Molecules with the potential target biological activity were analyzed in a validated *in silico* assay that is based on public domain National Cancer Institute *in vitro* anti-cancer data. The molecules are first decomposed to 110 descriptors using a proprietary CHEMSAS™ algorithm. This decomposition process results in a molecular data pattern of 110 variables that is then input into the *in silico* model. The output of the model is a prediction of the -Log(GI50) for the molecule(s) being analyzed against the specific cancer cell type in question i.e. breast cancer or leukemia, etc. A specific *in silico* assay was also developed for the leukemia cell line (i.e. K562) that over expresses the abnormal protein tyrosine kinase found in Chronic Myelogenous Leukemia (CML). Results of the *in silico* assay for molecular Formulas II and III in a number of cancer cell types are summarized below in Table 1.

Table 1

Compound	leukemia	K562(CML)*	NSCLC**	SCLC***	Colon	CNS
Formula II	-5.41	-5.66	-4.97	-4.79	-5.12	-5.02
Formula III	-5.43	-5.76	-5.04	-4.73	-5.3	-5.05
Formula IV		-5.7				

Compound	Melanoma	Ovary	Renal	Prostate	Breast
Formula II	-4.91	-5.0	-4.91	-5.17	-4.75
Formula III	-4.95	-4.99	-4.97	-5.86	-4.84

Note: Values in the table refer to the –Log(G150) as a molar concentration.
If –Log(G150)>-4.5 then the compound is likely to be inactive.
If –Log(G150)>-5 and <-4.5 then the compound is likely to have some *in vitro* activity.
If –Log(G150)<-5 then the compound is considered to have *in vitro* activity.
*K562 is a specific leukemia cell line for CML that over expresses the abnormal protein tyrosine kinase.
** NSCLC is a non small cell lung cancer
***SCLC is a small cell lung cancer

Example 2

Synthesis of the salt of Formula IV

Intermediate **1**

Intermediate **1** was prepared as shown in Scheme 2. Esterification of 4-bromomethylbenzoic acid **4** (25 grams) was carried out in refluxing methanol (500 ml) in the presence of concentrated H_2SO_4 (5 ml) to yield methyl 4-bromomethylbenzoate **5**. TLC (thin layer chromatography) monitoring of the reaction mixture showed formation, over time, of a side-product (about 15-20%), which according to ^{1}H-NMR analysis, was identified as methyl 4-methoxymethylbenzoate. The mixture of methyl 4-bromomethylbenzoate **5**

and the side-product (4.56 grams; 1 equiv) was reacted with commercially available 4-boc-aminopiperidine **6** (Aldrich™) (4.0 grams) in 100 ml of DCM or 100 ml of methanol in the presence of potassium carbonate (4.14 grams; 1.5 equiv) at room temperature to yield compound **7**. Reaction in methanol afforded compound **7**, as identified by ^{1}H NMR, in 72% yield compared to 57% obtained with DCM.

Compound **7** was refluxed with NaOH (1.5 eq) in methanol for 4-5 hours. The reaction mixture was cooled and 2.0 M HCl solution in ether was added to neutralize excess NaOH and convert the corresponding sodium carboxylate into the free acid. Then solvent was carefully removed in vacuum and the residue treated with water/DCM 1:1. Pure **8** crystallized at the water/DCM interface as a white solid, which was collected by filtration and air dried to give an 83.7% yield.

A mixture of **8** (1 gram), HBTU (O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate) (1.36 grams Cl (2 equiv)), DIPEA (N,N-diisopropylethylamine) (1.6 ml (3 equiv)) and DMF (dimethylformamide) (30 ml) was stirred at room temperature for four hours to form the activated ester **9** (42% yield). 2 equivalents of sodium 2-chloropyrid-4-ylamide (generated from the reaction of 4-amino-2-chloropyridine with sodium hydride) in DMF was added. The reaction mixture was separated by preparative TLC, and identified by ^{1}H NMR and MS as intermediate **1**.

Intermediate **2**

Intermediate **2** was prepared as shown in Scheme 3. For the transformation of 3-nitrobenzonitrile **11** into 3,4,5,6-tetrahydro-2-(3-nitrophenyl)-pyrimidine **12** (25% yield), a procedure described in European Patent Application 0225725 A1 (incorporated herein by reference) for 4-nitrobenzonitrile was used. 3-nitrobenzonitrile **11** (21 grams), sodium (0.32 grams, 0.1 equiv), diaminopropane (12 ml) and 190 ml of anhydrous ethanol was used. 3,4,5,6-tetrahydro-2-(3-nitrophenyl)-pyrimidine **12** (30 grams) was protected using Boc_2O (di-tert-butyl dicarbonate) (38 grams; 1.2 equiv), carried out in DCM (1.4 ml) at room temperature in the presence of DMAP (4-

dimethylaminopyridine) (0.9 grams; 0.05 equiv) as a catalyst to yield Boc-protected compound **13** (76% yield). The nitro group of compound **13** (21 grams) was reduced with a hydrazine hydrate (13.4 ml; 4.0 equiv) /Raney Ni (25 grams) system in 350 ml of ethanol at 50-75°C for about 30 minutes, which afforded Intermediate **2** in a 47% yield.

Salt of Formula IV

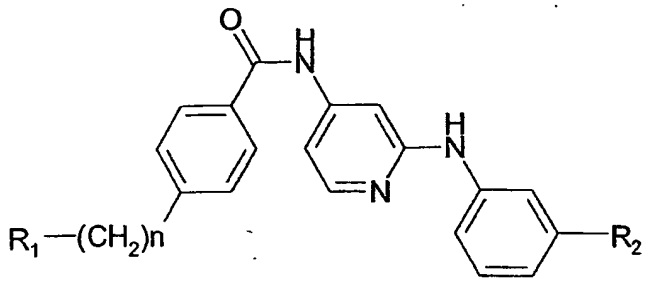
The salt of Formula IV was prepared as shown in Scheme 1. A mixture of 9 grams of intermediate **1** and 5.4 grams of intermediate **2** was prepared. 30 mol% $Pd(OAc)_2$ and 45 mol% BINAP (2,2'-bis(diphenyphosphino)-1,1'-binaphthyl) were employed in the reaction. After heating the reaction mixture for about 20 hours, the reaction was then worked up. In order to get rid of all non-basic impurities, and therefore diminish the amount of crude material needed to be purified, the reaction mixture was diluted with EtOAc and extracted with 5% HCl solution. The substrates and final product were separated into the acidic aqueous phase. The acidic phase was then neutralized with NaOH and basic components extracted with EtOAc. Concentration of the extracts afforded 13 g crude mixture in total. Compound **3** was separated using column chromatography (5-10% MeOH in DCM) to provide us with 0.9 g (6.5% yield) pure amide **3**. Finally, the Boc protective groups were removed using a saturated HCl solution in MeOH and the HCl salt of Formula IV was precipitated out with anhydrous ether to afford 0.58g (70% yield).

Although the ^{1}H-NMR spectrum of the HCl salt of Formula IV compared to that of compound **3**, the mass-spectrum of the HCl salt of Formula IV showed a single signal of the protonated molecular ion $[M+H^+]$=484 which corresponds to the free base of Formula IV.

Although preferred embodiments of the invention have been described herein in detail, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention.

We Claim:

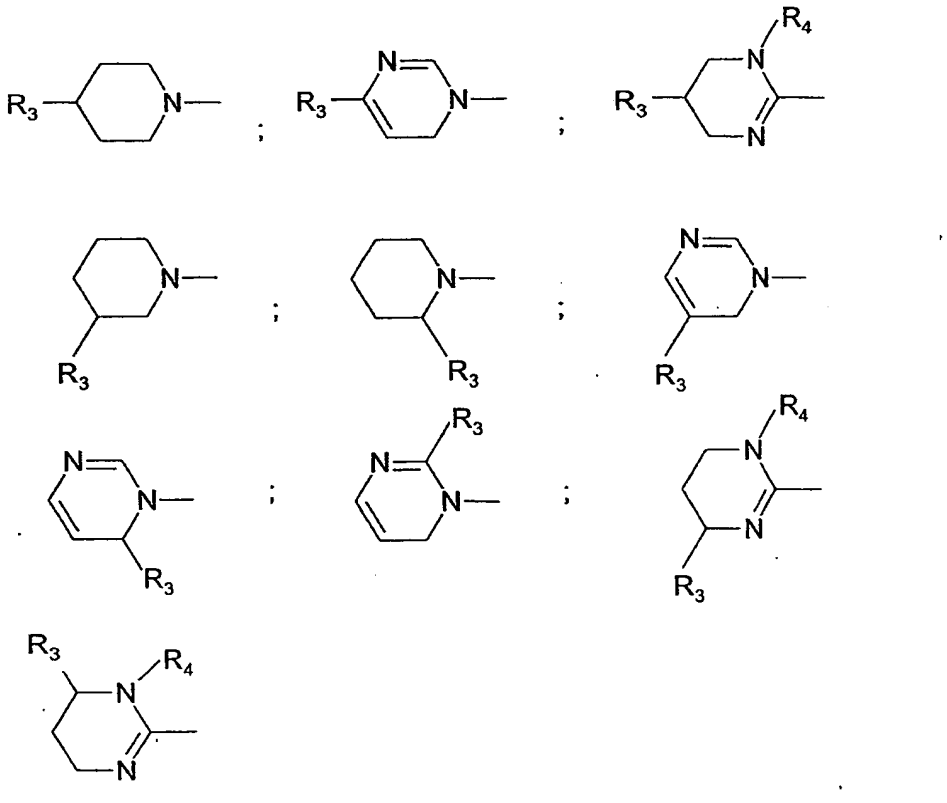
1. A compound selected from the group consisting of a compound of Formula I, a pharmaceutically acceptable salt thereof and a stereoisomer thereof:



Formula I

wherein n is an integer;

wherein R_1 and R_2 are independently selected from the group consisting of:



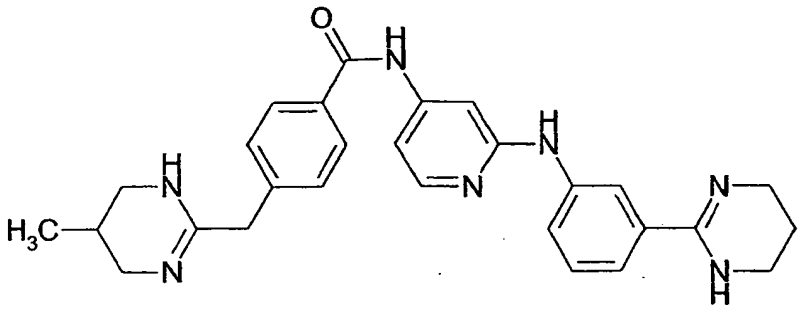
wherein R_3 is selected from the group consisting of H; alkyl; alkenyl; alkynyl; halogen; aryl; heteroaryl containing N, O, or S; NZ_1Z_2, wherein Z_1 and Z_2 are independently selected from the group consisting of H and alkyl; and (CO)Y wherein Y is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heteroaryl containing N, O, or S; and

wherein R_4 is selected from the group consisting of H and alkyl.

2. The compound of claim 1, wherein n is 1.

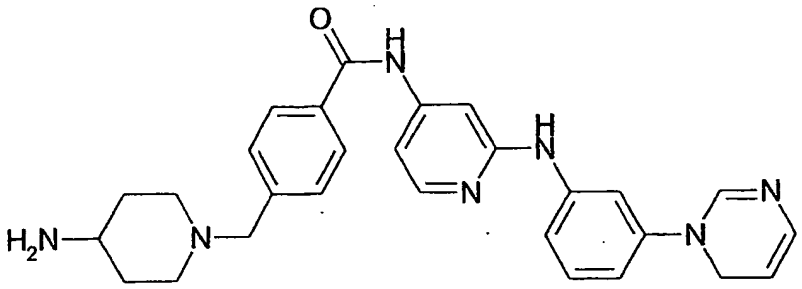
3. The compound of claim 1, wherein the aryl and heteroaryl are substituted with at least one of a halogen, an alkyl, an alkenyl, and an alkynyl.

4. The compound of claim 1, wherein the compound is selected from the group consisting of a compound of Formula II, a pharmaceutically acceptable salt thereof and a stereoisomer thereof:



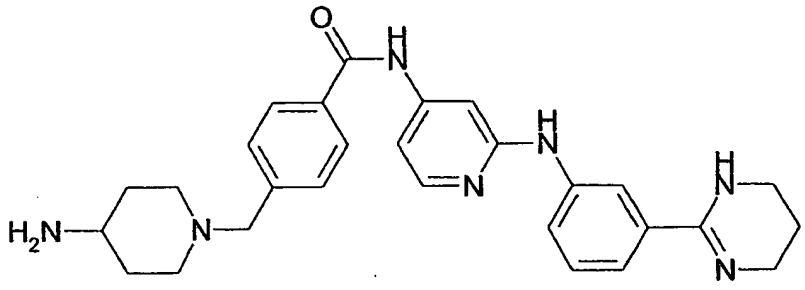
Formula II

5. The compound of claim 1, wherein the compound is selected from the group consisting of a compound of Formula III, a pharmaceutically acceptable salt thereof and a stereoisomer thereof:



Formula III

6. The compound of claim 1, wherein the compound is selected from the group consisting of a compound of Formula IV, a pharmaceutically acceptable salt thereof and a stereoisomer thereof:



Formula IV

7. The compound of any one of claims 1, 3, 4 and 5, wherein the pharmaceutically acceptable salt is derived from an inorganic acid or an organic acid, wherein the inorganic acid is selected from the group consisting of hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids; and the organic acid is selected from the group consisting of acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-

benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and trifluoroacetic acids.

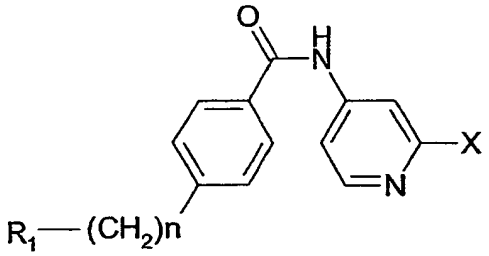
8. The compound of claim 7, wherein the pharmaceutically acceptable salt is derived from hydrochloric acid.

9. The compound of any one of claims 1, 4, 5 and 6, wherein the compound inhibits, regulates and/or modulates tyrosine kinase signal transduction.

10. The compound of claim 9, wherein the tyrosine kinase is a receptor-type and/or non-receptor type tyrosine kinase.

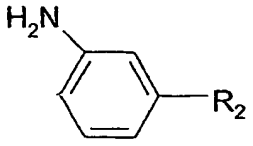
11. A pharmaceutical composition comprising the compound of any one of claims 1, 4, 5 or 6, or mixtures thereof, and a pharmaceutically acceptable carrier.

12. A method for making the compound of claim 1, comprising reacting



X= Cl, Br, F

with



in the presence of a palladium coupling catalyst for promoting carbon-nitrogen bond-forming cross-coupling.

13. The method of claim 12, wherein the palladium coupling catalyst is one of $Pd(OAc)_2$ with BINAP and $Pd_2(dba)_3$ with DPPF.

14. The method of claim 12 or 13, wherein the R_1 and/or R_2 groups contain protecting groups and the method further comprises a deprotection step.

15. A method of treating or preventing a tyrosine kinase-dependent disease or condition in a mammal in need of such treatment which is comprised of administering to the mammal a therapeutically effective amount of the compound of any one of claims 1, 4, 5 and 6, or mixtures thereof.

16. The method of claim 15, wherein the therapeutically effective amount is between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day.

17. The method of claim 16, wherein the therapeutically effective amount is between about 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

18. The method of claim 15, wherein the tyrosine kinase-dependent disease or condition is cancer.

19. A method of treating cancer in a mammal in need of such treatment which is comprised of administering to the mammal a therapeutically effective amount of the compound of any one of claims 1, 4, 5 and 6, or mixtures thereof, in combination with a therapy selected from the group consisting of radiation therapy and chemotherapy.

20. The method of claim 19, wherein the therapeutically effective amount is between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day.

21. The method of claim 20, wherein the therapeutically effective amount is between about 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

22. The method of claim 18 or 19, wherein the cancer is selected from the group of cancers consisting of cancers of the breast, leukemias, melanoma, stomach, colon, CNS, ovarian and prostate and lung.

23. The method of claim 18 or 19, wherein the cancer is chronic myelogic leukemia (CML).

24. Use of the compound of any one of claims 1, 4, 5 and 6, or mixtures thereof, for treating or preventing a tyrosine kinase-dependent disease or condition.

25. Use of the compound of any one of claims 1, 4, 5 and 6, or mixtures thereof, for treating cancer or preventing cancer.

26. The use of the compound of claim 25, wherein the cancer is selected from the group of cancers consisting of cancers of the breast, leukemias, melanoma, stomach, colon, CNS, ovarian and prostate and lung.

27. The use of the compound of claim 25, wherein the cancer is chronic myelogic leukemia (CML).

28. A process for making a pharmaceutical composition which comprises combining a compound of any one of claims 1, 4, 5 and 6, or mixtures thereof, with a pharmaceutically acceptable carrier.

29. Use of a compound of any one of claims 1, 4, 5 and 6, or mixtures thereof, in a medicament for the treatment or prevention of a tyrosine kinase-dependent disease or condition.

30. The use of the compound of claim 29, wherein the tyrosine kinase-dependent disease or condition is cancer, wherein the cancer is selected from the group of cancers consisting of cancers of the breast, leukemias, melanoma, stomach, colon, CNS, ovarian and prostate and lung.

31. The use of the compound of claim 30, wherein the cancer is chronic myelogic leukemia (CML).

32. A composition comprising a compound of any one of claims 1, 4, 5 and 6, or mixtures thereof, and a compound selected from the group consisting of an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic agent, an anti-proliferative agent, a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, and troponin-1, tamoxifen and raloxifene.

INTERNATIONAL SEARCH REPORT

Internatio plication No
PCT/CA 03/01162

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 A61K31/506 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02 22597 A (NOVARTIS ERFIND VERWALT GMBH ;BREITENSTEIN WERNER (CH); CARAVATTI) 21 March 2002 (2002-03-21) the whole document	1-32
A	WO 01 53274 A (AGOURON PHARMA) 26 July 2001 (2001-07-26) the whole document	1-32

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 2003	30/12/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/01162

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-27, 29 and 30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 03/01162

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0222597 A	21-03-2002	AU	1816702 A	26-03-2002
		BR	0113838 A	03-06-2003
		CA	2416274 A1	21-03-2002
		WO	0222597 A1	21-03-2002
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		EP	1252146 A1	30-10-2002
		JP	2003529558 T	07-10-2003
		WO	0153274 A1	26-07-2001
		US	2002103203 A1	01-08-2002